

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 983034WOTM	FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.					
International application No.	International filing date (day/mont	h/year) (Earliest)	Priority Date (day/month/year)			
PCT/HU 99/00102	23/12/1999		29/12/1998			
Applicant RICHTER GEDEON VEGY SZETI	GY R RT. et al.					
This international Search Report has been according to Article 18. A copy is being tra	n prepared by this international Sea ansmitted to the international Bureau	rching Authority and is L	transmitted to the applicant			
	of a total of she a copy of each prior art document o	eets. Ited in this report.				
Basis of the report With regard to the language, the language in which it was filed unit	international search was carried out ess otherwise indicated under this it	on the basis of the inte	emational application in the			
_	as carried out on the basis of a trans		nal application furnished to this			
	e sequence listing : nal application in written form.		application, the international search			
H	mational application in computer rea this Authority in written form.	idable form.				
	this Authority in computer readble for					
the statement that the sub- international application as	sequently furnished written sequent s filed has been furnished.	e listing does not go b	eyond the disclosure in the			
the statement that the info furnished	rmation recorded in computer reads	ble form is identical to	the written sequence listing has been			
	nd unsearchable (See Box I).					
3. Unity of invention is lack	ding (see Box II).					
4. With regard to the title,						
the text is approved as sub	omitted by the applicant.					
the text has been establish	ned by this Authority to read as folio	w 8 :				
5. With regard to the abstract,						
th text is approved as sub	omitted by the applicant.					
the text has been establish within one month from th	ned, according to Rul 38.2(b), by the date of mailing of this international a	ls Authority as it appea search report, submit c	ars in Box III. The applicant may, comments to this Authority.			
6. The figure of the drawings to be public	shed with the abstract is Figure No.					
as suggested by the applic			Non of the figures.			
because the applicant falle		·				
Decause this figure better of	characterizes th Invention.		·			



Ational Application No. /HU 99/00102

CLASSIFICATION OF SUBJECT MATTER PC 7 C07C227/04 C07C229/28 C07C205/51 According to international Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Category ° Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Y EP 0 414 274 A (GOEDECKE AG) 1,4,5 27 February 1991 (1991-02-27) cited in the application page 6 -page 12 Y BRYANS J S ET AL: "Investigation into the 1,4,5 preferred conformation of Gabapentin for interaction with its binding site on the alpha2delta subunit of a calcium channel" **BIOORGANIC & MEDICINAL CHEMISTRY** LETTERS, GB, OXFORD, vol. 7, no. 19, 7 October 1997 (1997-10-07), pages 2481-2484, XP004136469 ISSN: 0960-894X the whole document -/--X Further documents are listed in the continuation of box C. Patent family members are listed in annex. Special categories of cited documents: "T" later document published after the International filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not considered to be of particular relevance cited to understand the principle or theory underlying the Invention "E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention filina date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person sidiled "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but in the art. later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 23 March 2000 29/03/2000 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Rufet, J Fax: (+31-70) 340-3016

International Application No /HU 99/00102

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C.(Continu	Action) DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages	
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A	EP 0 414 263 A (GOEDECKE AG) 27 February 1991 (1991-02-27) abstract	1
A	EP 0 432 504 A (LONZA AG) 19 June 1991 (1991–06–19) abstract; claim 1	1
\	GARETH GRIFFITHS ET AL: "Novel Syntheses of Gabapentin via Addition of Hydrocyanic Acid to Cyclohexylidenemalonate or Cyano(cyclohexylidene)acetate" HELVETICA CHIMICA ACTA, CH, VERLAG HELVETICA CHIMICA ACTA. BASEL, vol. 74, no. 2, 1991, pages 309-314, XP002100736 ISSN: 0018-019X the whole document	1

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HU 99/00102

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					2120021 W	04-08-1992



## ORLD INTELLECTUAL PROPERTY ORGANIZA International Bureau



## RNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7: C07C 227/04, 229/28, 205/51

A1 (11) International Publication Number:

WO 00/39074

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PCT/HU99/00102

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(30) Priority Data:

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29 December 1998 (29.12.98) HU

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(72) Inventors; and

(75) Inventors/Applicants (for US only): GIZUR, Tibor [HU/HU]; Avarszállás u. 30, H-1162 Budapest (HU). LENGYEL, Zoltánné [HU/HU]; Zirzen J. u. 40/c., H-1125 Budapest (HU). SZALAI, Krisztina [HU/HU]; Sarkadi út 2. VI. em. 20., H-1039 Budapest (HU).

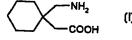
(74) Common Representative: RICHTER GEDEON VEGYÉSZETI GYÁR RT.; Gyömroi út 19-21, H-1103 -Budapest X. (HU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

### Published

With international search report.

(54) Title: PROCESS FOR THE SYNTHESIS OF 1-(AMINOMETHYL)CYCLOHEXYL-ACETIC ACID



NO₂

(II)

### (57) Abstract

The invention relates to a new process for the synthesis of 1-(aminomethyl)cyclohexyl-acetic acid of formula (I) via the new group or  $C_1$ - $C_4$  alkyl or alkoxy aromatic ring substituted derivatives thereof.

## FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL AM AT AU AZ BA BB BB	Albania Amenia Austria Australia Azerbaijan Bosnia and Herzegovina Barbados Belgium	ES FI FR GA GB GE GH GN	Spain Finland France Gabon United Kingdom Georgia Ghana Guinea	LS LT LU LV MC MD MG	Lesotho Lithuania Luxembourg Larvia Monaco Republic of Moldova Madagascar	SI SK SN SZ TD TG TJ	Slovenia Slovakia Senegal Swaziland Chad Togo Tajikistan
BG BJ BR CA CF CG CH CI CM CV CU CZ DE DK EE	Bulgaria Benin Brazil Belarus Canada Central African Republic Congo Switzerland Côte d'Ivoire Cameroon China Cuba Czech Republic Germany Denmark Estonia	HU IE IL IS IT JP KE KG KP KR LC LI LK LR	Hungary Ireland Israel Iceland Italy Japan Kenya Kyrgyzstan Democratic People's Republic of Korea Republic of Korea Kazakstan Saint Lucia Liechtenstein Sri Lanka Liberia	ML MN MR MW MX NE NL NO NZ PL PT RO RU SD SE SG	Republic of Macedonia Mali Mongolia Mauritania Malawi Mexico Niger Netherlands Norway New Zealand Poland Portugai Romania Russian Federation Sudan Sweden Singapore	TR TT UA UG US UZ VN YU ZW	Turkey Trinidad and Tobago Ukraine Uganda United States of America Uzbekistan Viet Nam Yugoslavia Zimbabwe

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C227/04 C07C229/28 C07C205/51 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07C Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Υ EP 0 414 274 A (GOEDECKE AG) 1,4,5 27 February 1991 (1991-02-27) cited in the application page 6 -page 12 Υ BRYANS J S ET AL: "Investigation into the 1,4,5 preferred conformation of Gabapentin for interaction with its binding site on the alpha2delta subunit of a calcium channel" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 7, no. 19, 7 October 1997 (1997-10-07), pages 2481-2484, XP004136469 ISSN: 0960-894X the whole document Further documents are listed in the continuation of box C. X Patent family members are listed in annex. Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not cited to understand the principle or theory underlying the considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention citation or other special reason (as specified) cannot be considered to involve an inventive step when the document is combined with one or more other such docudocument referring to an oral disclosure, use, exhibition or other means ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 23 March 2000 29/03/2000 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016

Rufet, J



onat Application No PCT/HU 99/00102

Category °	ation) DOCUMENTS CONSIDERED TO BE RELEVANT  Citation of document, with indication, where appropriate, of the relevant passages		
guiy	on account of the relevant passages		Relevant to claim No
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Α	EP 0 414 263 A (GOEDECKE AG) 27 February 1991 (1991-02-27) abstract		1
Α.	EP 0 432 504 A (LONZA AG) 19 June 1991 (1991-06-19) abstract; claim 1		1
A	GARETH GRIFFITHS ET AL: "Novel Syntheses of Gabapentin via Addition of Hydrocyanic Acid to Cyclohexylidenemalonate or Cyano(cyclohexylidene)acetate" HELVETICA CHIMICA ACTA, CH, VERLAG HELVETICA CHIMICA ACTA. BASEL, vol. 74, no. 2, 1991, pages 309-314, XP002100736		1
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## **PCT**

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### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or ag	ent's file reference	T		Notification of Transmittal of	International			
983034WOTI	M	FOR FURTHER AC	ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)					
International app	lication No.	International filing date (	day/month/year	Priority date (day/mo	onth/year)			
PCT/HU99/00	)102	23/12/1999		29/12/1998				
International Pate C07C227/04	ent Classification (IPC) or na	tional classification and IPC						
Applicant								
RICHTER GE	DEON VEGYESZETI	GYAR RT. et al.						
	ational preliminary exami smitted to the applicant a		prepared by t	nis International Preliminar	y Examining Authority			
2. This REPO	ORT consists of a total of	5 sheets, including this	cover sheet.					
been a (see R	eport is also accompanied amended and are the bas ule 70.16 and Section 60 exes consist of a total of	is for this report and/or 7 of the Administrative	sheets contai	cription, claims and/or dra ning rectifications made be nder the PCT).	wings which have fore this Authority			
3. This report	contains indications rela	ting to the following iten	ns:					
ı 🗵	Basis of the report							
	Priority							
III 🗆			velty, inventiv	e step and industrial applic	ability			
V ⊠	Lack of unity of invention Reasoned statement uncitations and explanation	nder Article 35(2) with re	egard to nove	y, inventive step or industi	rial applicability;			
VI ⊠	Certain documents cite	ed .						
VII 🗆	Certain defects in the in	ternational application						
VIII 🗵	Certain observations on	the international applic	ation					
Date of submission	n of the demand		Date of compl	ition of this report				
14/07/2000			31.10.2000					
Name and mailing address of the international preliminary examining authority:  European Patent Office  Authorized officer								

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU99/00102

I.	Basis	of the	report
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<ol> <li>This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):</li> </ol>									ice in d to						
	De	scription, pages:													
	1-6	:	as origin	ally fil	ed										
	Cla	ims, No.:													
	1-6		as origin	ally fil	ed										
2.		e amendments have			cance	llation o	of:								
		the description,	pages Nos.:	<b>5</b> :			·	<del></del>	<del></del>	<del></del>					
		the drawings,	sheets	s:											
3.		This report has beconsidered to go b	en establ eyond th	ished e disc	as if (se	ome of) as filed	) the amer (Rule 70.	ndment 2(c)):	s had no	ot been	made,	since	they h	iave b	een
4.	Ado	litional observations	, if neces	ssary:											
V.	Rea app	isoned statement ι licability; citations	under Ar and exp	ticle 3 olanat	5(2) wi	ith rega upporti	ard to no	velty, iı statem	nventive ent	e step c	r indu	strial	ı		
1.	Stat	ement													
	Nov	relty (N)	Ye: No		Claims Claims	1-6									
	Inve	entive step (IS)	Ye: No:		Claims Claims	1-6									
	Indu	ustrial applicability (I	A) Yes No:		laims laims	1-6									



2. Citations and explanations

see separate sheet

#### VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

### VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

### SECTION V

D1= EP-A-0 414 274

- 1. The present application relates to a process for producing 1-(aminomethyl)cyclohexyl acetic acid (gabapentin) and the intermediates used therein.
- Document D1 cited in the description on pages 1 and 2 is considered to represent 2. the closest state of the art. It discloses a process for the preparation of gabapentin starting from cyclohexanon and using ethyl cyclohexylidene acetate and 2-azaspiro[4,5]decane-3-on (lactam derivative) as key intermediates. The lactam is subsequently hydrolysed to gabapentin hydrochloride which is transformed into the final product by means of a ion-exchange resin (see D1, pp. 6-8 and Examples). The problem to be solved by the present application with respect to this prior art is to provide an alternative/improved process for the production of a gabapentin.
- The process of present claim 1 differ from the known method essentially in that it 3. employs new intermediates represented by the formulae IIa and IIb. Surprisingly, catalytic hydrogenation of these compounds directly yields gabapentin without any lactam formation, thereby making the labour-demanding and expensive ionexchange separation superfluous.
  - Accordingly, the subject-matter of claim 1 meets the requirements of Article 33(2)(3) PCT.
- 4. Dependent claims 2-5 concern particular embodiment of claim 1. They fulfil the requirements of Art. 33(2) and (3) PCT as well.
- 5. The compounds of 6 and 7 are novel intermediates in the process of claim 1. Thus, claims 6 and 7 also meet the requirements of Article 33(2)(3) PCT.

### **EXAMINATION REPORT - SEPARATE SHEET**

**SECTION VI** 

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Certain published documents (Rule 70.10)

Application No Patent No

Publication date (day/month/year) Filing date

Priority date (valid claim)

(day/month/year)

(day/month/year)

WO9921824

06.05.99

23.09.98

27.10.97

and24.08.98

### **SECTION VIII**

- The process according to claim 1 for the production of a pharmaceutically accep-1. table salt of gabapentin is not supported by the description as required by Article 6 PCT.
- 2. The definition of X in the reagent R₁-X (cf. claim 1) has been omitted from the description. Hence, claim 1 does not meet the requirements of Article 6 PCT.



### **PCT**

### **NOTIFICATION OF ELECTION**

(PCT Rule 61.2)

### From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
11 August 2000 (11.08.00)

International application No.
PCT/HU99/00102

International filing date (day/month/year)
23 December 1999 (23.12.99)

Applicant

GIZUR, Tibor et al

1.	The designated Office is hereby notified of its election made:
	X in the demand filed with the International Preliminary Examining Authority on:
	14 July 2000 (14.07.00)
	in a notice effecting later election filed with the International Bureau on:
2.	The election X was
	was not
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer

Maria Kirchner

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35